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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/045,721	10/26/2001	Naohiro Terada	5853-207	9675

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AKERMAN SENTERFITT
P.O. BOX 3188
WEST PALM BEACH, FL 33402-3188

EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 12/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/045,721	TERADA ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,6,8 and 14-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,6,8 and 14-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and argument of 10/12/05 is entered.

Claims 2, 4, and 10-13 have been cancelled.

Claims 1, 3, and 5-6 have been amended.

Claims 1, 3, 5-6, 8, and 14-20 are presently pending and considered.

Note: Change in Art Unit and SPE

The Examiner has been reassigned to Art Unit 1633. Therefore, future correspondence should reflect such changes. Also, at the end of the Action is the information regarding the SPE of the Art Unit.

Rejections of Canceled Claims

In light of Applicant's cancellation of claims 2, 4, and 10-13, all rejections and objections to such claim are rendered moot, and thus, are withdrawn.

Claim Objections

Claim 1 is objected to because of the following informalities: embryonic stem cell has an improper article. The proper is article is "an", not "a".

Claim 1 is objected to for the limitation "and the second subculture with the second test substance". The proper article for such limitation is "a second test substance".

Claim 1 is objected to for the recitation of "culturing the first and second subcultures between 7 to 18 days". As it is clear that Applicant means "for 7 to 18 days", this is not rejected

for lack of clarity, however, proper correction is required to reflect proper English. Amending the limitation to recite "culturing the first and second subcultures for 7 to 18 days" would be remedial.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In light of Applicant's amendment and argument, the rejections of Claims 1, 3, 5-6, 8, and 14-20 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, are withdrawn; however the following new basis of rejection are applied.

Claim 1 recites "a method for identifying a drug candidate for promoting tissue-specific differentiation of a embryonic stem cell" which comprises exposing two subcultures to distinct test substances, then exposing each subculture to two more differentiation test substances. As such, it appears that the test substances initially exposed are no longer the differentiation test substance, as there exist two more test substances which are named "differentiation test substance", and further, at best, the method identifies two, if not three, substances that induce differentiation. Hence, there appears to be an absence of a nexus between the claimed method in the preamble, and a step of identifying a test substance that promotes differentiation.

Claim 1 also recites the limitation "undifferentiated embryonic stem cells". As embryonic stem cells are necessarily not differentiated, otherwise they would be called the cell type which it has differentiated into, the metes and bounds of such limitation are unclear.

Claims 3 and 5-6 recites the limitations "the embryonic stem cells", "the murine embryonic stem cells", and "the mammalian embryonic stem cells", respectively, in claim 1. There is insufficient antecedent basis for this limitation in the claim. Specifically, it is noted that the cells of claim 1 are undifferentiated embryonic stem cells, and not limited to mammalian or murine either.

Claim 8 recites the "the conditions that would promote tissue-specific differentiation of stem cells" in claim 1. However, there is insufficient antecedent basis for this in claim 1. Moreover, it is unclear whether and when the subcultures are cultured in the conditions are before, during or after exposure to the various test substances, hence, the claim further lacks clarity for this aspect.

Claims 3, 5-6, 8, and 14-20 are also rejected for depending for depending rejected base claim(s) and not overcoming the lack of clarity in such base claim.

Claim Rejections - 35 USC § 112 – new matter

While the previous rejections of Claims 1-6, 8, and 10-20 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for new matter are withdrawn, the following new basis of rejection is applied, due to the amendments.

Claims 1, 3, 5-6, 8, and 14-20 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for reasons necessitated by

amendment. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Simply put, claim 1 is drawn to a method to identify a drug candidate for promoting tissue-specific differentiation of an embryonic stem cell, comprising culturing at least two subclones of an undifferentiated embryonic stem cell population for at least about 3 days (which is new matter again, but now applied differently from the previous rejection due to the extensive amendment to the claims), exposing each subclone to distinct test substances, culturing the cells for 7-18 days, wherein during days 9-12, a first differentiation test substance is added, and on days 12-18 a second differentiation test substance is added, then analyzing the cells for any increased tissue-specific gene expression. Nowhere in the specification or claims as filed is there implicit or explicit support for such a group of embodiments, or even a single embodiment embraced by the group.

However, pages 15-16 discuss a specific experiment which parallels many of the aspects of the claims. To wit, after observing various markers for hepatocyte differentiation in mouse embryonic stem cells (p. 15), it was noted that the cells being used did not differentiate into mature hepatocytes, only immature forms of hepatocyte lineage (p. 15). However, Applicant performed an experiment, based on the knowledge of *in vivo* differentiation of mouse ES cells and the factors known to be involved in hepatic maturation of such cells, in order to model the system *in vitro* (pp. 15-16, paragraph bridging). Such factors are known to be FGFs at day 9 (Id.), HGF at a later stage (Id.), and oncostatin M at a third stage in time (Id.). Based on these timings, Applicant cultured the EB cells, derived from ES cells, *in vitro*, to add aFGF from day

9-12, HGF on days 12-18, and Oncostatin M, as well as a mixture of other factors, on days 15-18, and from the resultant cells, the patterns of hepatic lineage gene expression were analyzed. (p. 16, paragraph 2). Moreover, Applicant calls aFGF "an early stage factor potentially inducing hepatic differentiation", while HGF is added "as a midstage factor", and the other factors are added "as late stage factors".

While calling aFGF a factor potentially inducing hepatic differentiation, such does not make this method a screen for any factor, but simply a test to determine if the system could be modeled *in vitro*. The Artisan would simply read the use of "potentially" with regard to FGF to mean that there exist many FGFs and Applicant simply tried this particular candidate because they expected it to work. Moreover, the other factors are not called "potential" factors, but are simply "a" factor inducing differentiation at that particular stage. Further, even if FGF were determined to be explicit support for any factor, it is added on days 9-12, which necessarily means that the other factors are not factors which are being screened, yet, apparently, the factor added from days 12-18 is a test substance for differentiation. Further, this example discloses mouse EB cells, not undifferentiated embryonic stem cells, much less from any species. Lastly, the disclosure does not provide any support for the initial test substance added and cultured for 3 days.

Also, Applicant's closest support in the original specification and claims is by way of example, and as such, only provides support for the specific example provided, as obviousness does not substitute for written description. However, Applicant's claims are lacking in claiming the same subject matter. For example, the claims do not require any addition of the oncostatin and other factors which are added from days 15-18, nor does Applicant's claims require a full 18

days, but only 7-18 days, and they also require subcultures, another test substance, apparently added before EB cells are formed, and lastly, the cells are not of the same scope as the disclosure. Although these are provided by way of Example, many other aspects are not drawn to the same scope as that which is disclosed.

Similarly, it is also noted that at no point are the cells cultured for at least about 3 days, but only at least about 5 (SPECIFICATION, p. 16, paragraph 2). And hence, even in this context this is new matter.

In the end, it is clear that Applicant's support for the instant invention is not commensurate with what is claimed, or even encompassing common embodiments, due to the requirement of other factors, etc. Hence, these claims are rejected for claiming new matter.

Response to Argument – new matter

Applicant's argument of 10/12/05 has been fully considered but is not found persuasive.

Applicant argues that p. 16, paragraph 2 provides support for claimed method (Applicant's argument of 10/12/05, p. 7, paragraph 1).

Such is not persuasive, for the reasons given above.

Applicant argues that p. 9 of the specification provides support for the claimed invention with regard to culturing two subcultures for at least about 3 days prior to addition of a test substance is supported (Applicant's argument of 10/12/05, p. 7, paragraphs 2-3).

Such is not persuasive. Figure 2 is a specific example, and it took 5 days, not at least about 3 days. Hence, the scope is not the same. The further extrapolation to three days is not changed by fact that conditions vary between cells, Applicant should just claim at least about 5 days then, because if 5 days can mean Applicant contemplated at least about 3 days, then about 5

days can mean 3 days, or even not waiting at all. Also, again, Applicant's specific example cultures the cells, although not subdivided, for 5 days before doing anything at all (specification p. 16, paragraph 2). In the end, Applicant has simply not contemplated the specific claimed embodiment. Applicant is reminded that obviousness does not substitute for written description, or its ugly child, new matter, which we have here.

Therefore, the new matter rejection is newly applied.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5-6, 8, and 14-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's claims are drawn to identifying a compound, but the complicated protocol uses at least four distinct compounds in various combinations, to identify differentiation compounds, hence, at best, it could only produce a pool of compounds, of which one is a potential compound for differentiation.

Next, Applicant's claims are drawn to using any undifferentiated ES cells, yet clearly mouse EB cells are used in the methods (p. 16). Moreover, the claims are drawn to any

differentiation, yet, the disclosure is the induction of hepatocyte differentiation in such mouse EB cells, and no other differentiation pathway is disclosed to be produced in the method.

However, the Art generally recognizes that such differentiation is specific to the type of ES cell, or any cell for that matter, due to the complexities of the pathways, which may differ between species as well as within any pathway. Hence, the conditions and timings of adding the different factors would necessarily differ. While this may not matter for something as simple as a single stage of differentiation, Applicant's claims encompass many stages, and due to the forgoing differences in conditions required, any specific cell type could not be possible, or may form the differentiated cell type before any candidate drugs are even added. For example, U.S. Patent No. 6,485,589 to Rambhatla discloses specific conditions where the cells automatically differentiate into hepatocytes by the addition of a single compound (EXAMPLE 1). Hence, the other additions would not be able to go through the other stages of differentiation, as they would have developed into hepatocytes on day 1. In addition, Ramblata uses human EB cells. Hence, for any particular type of cell and conditions, such differentaitons may not take place through various stages, but may occur in a single stage and even before the addition of the compounds, as the growth conditions are distinct for any particular ES cell. Hence, using Applicant's method would not produce its desired result under optimal conditions, and further would require extensive experimentation to determine the set of conditions for any specific ES cell.

Therefore, it would be undue experimentation to find the conditions required for specific combinations of compounds required to produce, in the time frames given, hepatocytes or any other specific cell types.

Because of the undue experimentation, which would essentially amount to inventing Applicant's claimed subject matter for Applicant, Applicant's claimed invention is not enabled.

Claim Rejections – 35 USC § 103 – Liu/Keller

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

In light of Applicant's amendments, the rejections of Claims 1, 3, 6, 8 and 14-19 under 35 U.S.C. 103(a) as being unpatentable over Liu and further in view of U.S. Patent No. 5,874,301 to Keller, for reasons of record are withdrawn.

Simply put, nowhere in the art is it taught or obvious to perform such a complicated protocol to identify a candidate compound for inducing differentiation.

Claim Rejections – 35 USC § 103

In light of Applicant's amendments, the rejection of Claim 5 under 35 U.S.C. 103(a) as being unpatentable over Liu and Keller as applied to claim 1 above, and further in view of Kondoh, et al. (May, 1999) J. Biochem. Biophys. Meth., 39: 137-142, is withdrawn.

Simply put, nowhere in the art is it taught or obvious to perform such a complicated protocol to identify a candidate compound for inducing differentiation.

Claim Rejections – 35 USC § 103

In light of the amendments, the rejection of Claim 20 under 35 U.S.C. 103(a) as being unpatentable over Liu and Keller as applied to claim 1 above, and further in view of U.S. Patent No. 5,143,854 to Pirrung, is withdrawn.

Simply put, nowhere in the art is it taught or obvious to perform such a complicated protocol to identify a candidate compound for inducing differentiation.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert M. Kelly, Ph.D.
Examiner, USPTO, AU 1633
2C55 Remsen Building
(571) 272-0729